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REVIEW

Japanese regulation of biosimilar products: past experience and current challenges

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Seven biosimilar products have been approved in Japan since the March 2009 publication of the 'Guideline for quality, safety and efficacy assurance of biosimilar products' by the Ministry of Health, Labor and Welfare (MHLW). Four years previously, the 'Guideline on similar biological medicinal products' was issued in the European Union (EU), and 13 products as of February 2016 have been approved as biosimilar. The US Food and Drug Administration (FDA) approved the first biosimilar product in the US in March 2015 and final Guidance was issued at the end of April 2015. Over the past decade, the challenges regarding the development of biosimilar products have been discussed extensively. In this article, the data packages of biosimilar products in Japan are compared with those overseas in order to clarify the concepts used by the Japanese regulatory authority, i.e., the Pharmaceuticals and Medical Devices Agency (PMDA). The challenges in the development of biosimilar products in Japan are also addressed.

Introduction

The expiration of patents and/or data protection for the originators' biotechnology-derived products and the high cost of these products have promoted the development of biosimilar products, which are intended to be highly similar to reference biological products such that any differences in quality attributes do not affect safety or efficacy [1]. Biosimilar products rely for their licensing on accumulated information regarding the safety and efficacy obtained from the reference products. The amount and extent of data required for the licensing of biosimilar products is likely to be less than is normally required for the reference products.

A Japanese regulatory authority, the Ministry of Health, Labor and Welfare (MHLW), has been confronted with the challenge of regulating biosimilar products, and in March 2009 the MLHW issued a 'Guideline for the quality, safety and efficacy assurance of biosimilar products' [2]. Since then, seven biosimilar products including somatropin BS [3], epoetin alfa BS [4], filgrastim BS [5–7], infliximab BS [8] and insulin glargine BS [9] have been approved in Japan. In December 2015, the MHLW issued new Questions and Answers (Q&A) for a better understanding of the guideline [10].

In the European Union (EU), since the 2005 publication of the 'Guideline on similar biological medicinal products' by the European Medicines Agency (EMA) [11], 20 biosimilar products have European Commission marketing authorization as of 20 February 2016. They correspond to 13 different products as an identical data package may be submitted through several marketing authorization holders under several different commercial names. Other relevant guidelines have also been issued and revised based on the experiences obtained by the EMA regarding their Scientific Advice and the EMA's Marketing Authorization Applications (MAAs).

The US Food and Drug Administration (FDA) approved the first biosimilar product in the US, filgrastim BS [12] in March 2015, and in late April 2015 the FDA issued the publication 'Scientific considerations in demonstrating biosimilarity to a reference product' [13].

Over the past decade, the challenges regarding the development of biosimilar products have been discussed extensively. These challenges include not only development strategies but also the real-world use of biosimilar products [14]. This paper compares the data packages of biosimilar products in Japan with those overseas in order to clarify the concept of the Japanese

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regulatory authority, i.e., the Pharmaceuticals and Medical Devices Agency (PMDA). The challenges in the development of biosimilar products in Japan are also addressed.

Data packages of biosimilar products

In the Japanese Guideline for the development of biosimilar products, sponsors are required to establish their own manufacturing process, to clarify the quality attributes and to demonstrate the high similarity of these attributes to the reference products. In addition, the data of both clinical and non-clinical studies are required to demonstrate the biosimilar comparability [2, 15]. The data packages of biosimilar products approved in Japan are summarized in Table 1.

A main component of the development process of biosimilar products is clinical studies. The Japanese guideline basically requires that sponsors of biosimilar products demonstrate a pharmacokinetics (PK) profile that is similar to that of the reference product by all routes of administration used for the reference product. The guideline recommends that similarity is also demonstrated by using a pharmacodynamic (PD) marker relevant to the clinical outcome whenever feasible. It is usually necessary to demonstrate comparable clinical efficacy of biosimilar product in a confirmatory clinical trial, but in certain cases comparative PK/PD studies may be sufficient to demonstrate clinical comparability. This is also the

Table 1

Data package of biosimilar products approved in Japan

	Biosimilar GL	Somatropin BS	Epoetin alfa BS	Filgrastim BS F & Mochida	Filgrastim BS NK & Teva	Filgrastim BS Sandoz	Infliximab BS	Insulin glargine BS
Quality								
Characterization	○	○*	○*	○*	○*	○*	○*	○*
Manufacturing process	○	○	○	○	○	○	○	○
Specification	○	○	○	○	○	○	○	○
Stability								
Long-term test	○	○	○	○	○	○	○	○
Stress test	△	—	○	○*	○	○	○	○
Accelerated test	△	○	○	○*	○	○	○	○
Pharmacology								
Primary PD	○	○*	○*	○*	○*	○*	○*	○*
Safety Pharmacology	—	—	○	—	○	—	—	—
Others	—	—	—	—	—	—	—	—
PK								
ADME (non-clinical)	△	----	○* ○○○	----	○---	○---	○*---	○*---
BE (human)	—	—	—	—	—	—	—	—
Others	△	—	—	—	—	—	—	—
Toxicology								
Single-dose toxicity	△	○	○	○	○	—	○	○
Repeat-dose toxicity	○	○	○	○*	○	○	○*	○*
Genotoxicity	—	—	○	—	—	—	—	—
Carcinogenicity	—	—	—	—	—	—	—	—
Reproductive and developmental	—	—	○	—	—	—	—	—
Local tolerance	△	○*	○	○*	○	○	○*	○*
Others	△	—	—	—	○	—	—	—
Clinical								
Clinical studies	○	○*	○*	○*	○*	○*	○*	○*

*Comparative studies were included.

case in other regions/countries, although there are some differences. The clinical data packages of individual biosimilar products approved in Japan are described in detail below.

Somatropin BS

The data package of Somatropin BS 'Sandoz', which is the same product as Omnitrope, consists of a comparative PK study with the reference product Genotropin in healthy Japanese volunteers as the evaluation data, and comparative PK studies in healthy volunteers and Phase III studies of growth hormone deficiency (GHD) in paediatric populations conducted in other countries as reference/supportive data for the Japanese MAA, as described [3, 16]. In their review report, the PMDA seemed to attach importance to the comparative Phase III study for the evaluation of clinical comparability.

Epoetin alfa BS

Epoetin alfa BS 'JCR' was originally developed in Japan [4]. The reference product of epoetin alfa BS, Espo (750 IU, 1500 IU, 3000 IU), has two indications, 'renal anaemia in dialysis' and 'anaemia of prematurity', with intravenous (IV) and subcutaneous (SC) routes of administration, respectively. Therefore, comparative PK studies were conducted in renal anaemia patients on haemodialysis by IV administration and in healthy volunteers by SC administration (Table 2). Although the 90% confidence interval (CI) of the area under the curve (AUC) and the C_{max} values were without equivalence margins, Epoetin alfa BS was approved because the 95% CI of absolute change in the haemoglobin level, which is the primary endpoint of the comparative Phase II/III study in haemodialysis patients, was within the predefined acceptance range (Table 3).

For the epoetin alfa BS and epoetin zeta products approved in the EU [17, 18], comparative PK studies with the reference product Eprex/Erypo were conducted in healthy volunteers by both IV and SC administration (Table 2). In addition, comparative Phase III studies of renal anaemia patients on haemodialysis and studies of patients with anaemia due to cancer chemotherapy were conducted (Table 3). In Japan, the use of the reference product Espo is not approved for the indication of cancer chemotherapy-induced anaemia.

Filgrastim BS

Three filgrastim BS products have been approved in Japan: filgrastim BS 'F' and 'Mochida' [5], originally developed in Japan; filgrastim BS 'NK' and 'Teva' [6], which is a different formulation of the same substance as that in Tevagrastim;

Table 2

PK/PD studies of Epoetin alfa BS approved

	Japan	EU	
Product	**Epoetin Alfa BS 'JCR'**	**Abseamed, Binocrit, Epoetin alfa Hexal**	**Retacrit, Silapo**
Non-comparative study	Study JR-013H-101:	Study INJ-7 (supportive):	
	▪ single-blind, placebo-controlled	▪ single arm	
	▪ single IV	▪ multiple SC	
	▪ 24 healthy volunteers ♂(Japanese)	▪ 6 healthy volunteers	
Comparative study		Study INJ-4 (pilot):	
		▪ randomized, open, crossover	
		▪ single IV and SC	
		▪ 6 healthy volunteers	
		Study INJ-6:	
		▪ single and multiple SC	
		▪ 72 healthy volunteers	
	Study JR1102:	Study INJ-5:	Study 05–05:
	▪ open-label, crossover	▪ randomized, open, parallel-group	▪ 2-period, crossover
	▪ single IV	▪ multiple IV	▪ single IV
	▪ 24 hemodialysis patients (Japanese)	▪ 76 healthy volunteers ♂	▪ 24 healthy volunteers
	Study JR2101:	Study INJ-12:	Study 03–09:
	▪ open-label, crossover	▪ randomized, open, parallel-group	▪ 3-period, crossover
	▪ single IV	▪ multiple SC	▪ single SC (BS, Erypo), single IV (BS)
	▪ 32 healthy volunteers ♂(Japanese)	▪ 74 healthy volunteers ♂	▪ 48 healthy volunteers

Table 3

Phase III studies for Epoetin alfa BS approved

	Japan	EU	
Product	**Epoetin Alfa BS 'JCR'**	**Abseamed, Binocrit, Epoetin alfa Hexa**	**Retacrit, Silapo**
Renal anemia (IV)			
Comparative study	Study JR1301: ▪ double-blind, 24 weeks ▪ 24 hemodialysis patients (Japanese)	Study INJ-9: ▪ randomized, double-blind, parallel-group, 28 weeks (+ safety study, total 56 weeks) ▪ 478 hemodialysis patients	Study 04–04 (Maintenance phase): ▪ randomized, double-blind, crossover, 24 weeks ▪ 402 hemodialysis patients
			Study 04–05 (correction phase): ▪ randomized, double-blind, parallel-group, 24 weeks ▪ 609 hemodialysis patients
Long-term/safety study	Study JR1302: ▪ open-label, 52 weeks ▪ 143 hemodialysis patients (Japanese)		Study 04–14 (supportive): ▪ open-label, uncontrolled, 28 week interim ▪ safety trial with focus on anti-EPO antibodies ▪ 745 patients
Chemotherapy induced-anemia (SC)		Study INJ-11: ▪ randomized, double-blind 12 weeks (non-comparative controlled study, Erypo: measure of internal validity) ▪ 114 cancer patients	Study 04–46: ▪ uncontrolled, 12 week interim ▪ safety trial to provide information on thrombotic events ▪ 216 cancer patients

and filgrastim BS 'Sandoz' [7], a different formulation of the same substance as that in Zarzio. Comparative PK studies of all of the filgrastim BS products were conducted in healthy volunteers using both IV and SC administration because the reference product of filgrastim BS, Gran, has these two routes of administration, IV and SC (Table 4). The indications for Gran are based on its 'neutrophil increasing effect' and 'mobilization effects on the haematopoietic stem cells in peripheral blood'. The PD markers related to these effects are thought to be the absolute neutrophil count (ANC) and the $CD34^+$ cell count, respectively. Therefore, the clinical similarity of filgrastim BS was demonstrated by comparative PD studies in healthy volunteers by using these PD markers as primary endpoints, in addition to PK studies.

A single-arm Phase III study of Japanese breast cancer patients was also included in the data package of filgrastim BS 'F' and 'Mochida' [5] as evaluation data (Table 5). Three comparative Phase III studies conducted using Tevagrastim in countries other than Japan were included in the data package of filgrastim BS 'NK' and 'Teva' [6], and a single-arm Phase III study conducted using Zarzio in countries other than Japan is included in the data package of filgrastim BS 'Sandoz' [7]. In their review report, the PMDA evaluated only the safety of these reference/supportive data.

In filgrastim BS products approved in the EU [19–22], the clinical similarity with the reference product Neupogen was demonstrated by comparative PK studies of healthy volunteers by both IV and SC administration, and by comparative PD studies in healthy volunteers. The primary endpoint of the repeated-dose comparative PD studies was the ANC in the EU, whereas it was the $CD34^+$ cell count in Japan. Comparative or single-arm Phase III studies are also included in the data package of all of the filgrastim BS products (Table 6), as is the case in Japan.

In the US, the first biosimilar product Zarxio (filgrastim-sndz, which is the same product as Zarzio) was approved in 2015. The data package of Zarxio includes four PK/PD studies in healthy volunteers by SC administration only, three of which were conducted using EU-approved Neupogen as a comparator, and a comparative Phase III study between the biosimilar and the US-licensed Neupogen in breast cancer patients [12]. On the other hand, the Phase III study included in the data package of Zarzio for the EU's MAA is a single-arm study.

Infliximab BS

PD markers of infliximab are not established as surrogates for efficacy. Therefore, in the EU [23] and Canada [24], the clinical data package consists of a comparative PK study with the reference product Remicade for rheumatoid arthritis (RA) patients (a pilot test), a comparative PK study of ankylosing spondylitis (AS) patients and a comparative Phase III study of RA patients, the primary endpoint of which was the ACR 20 at week 30 (Table 7). For the Japanese MAA, a comparative PK study of RA patients conducted in Japan and a Phase III study of RA patients were provided as the evaluation data, and a pilot PK study of RA patients and a PK study of AS patients as reference/supportive data [8].

Table 4

Comparative PK/PD studies of filgrastim BS conducted in Japan

	Endpoint	Filgrastim BS 'F' & 'Mochida'	Filgrastim BS 'NK' & 'Teva'	Filgrastim BS 'Sandoz'
IV	PK	Study FSK0808P-03*: Double-blind, single dose (200 μg m^{-2}) 24 healthy volunteers ♂(Japanese)	Study PK-IV300: Single-blind, single dose (300 μg) 20 healthy volunteers ♂(Japanese)	
		Study FSK0808P-05: Double-blind, single dose (200 μg m^{-2}) 24 healthy volunteers ♂(Japanese)		Study EP06–107: Double-blind, single dose (2.5 μg kg^{-1}) 24 healthy volunteers ♂(Japanese)
	ANC			Study EP06–107
SC	PK		Study PK-SC150: Single-blind, single dose (150 μg) 30 healthy volunteers ♂ (Japanese)	
		Study FSK0808P-01: Open-label, single dose (400 μg m^{-2}) 40 healthy volunteers ♂(Japanese)	Study PK-SC300: Single-blind, single dose (300 μg) 30 healthy volunteers ♂(Japanese)	Study EP06–106: Double-blind, single dose (5 μg kg^{-1}) 24 healthy volunteers ♂(Japanese)
	ANC	Study FSK0808P-01	Study PD-SC300 single-dose: Single-blind, single dose (300 μg) 30 healthy volunteers ♂(Japanese)	Study EP06-106
	CD34	Study FSK0808P-04: Double-blind multiple dose (400 μg m^{-2} × 5 day) 42 healthy volunteers ♂(Japanese)	Study PD-SC300 repeated-dose: Single-blind, multiple dose (300 μg/day) 60 healthy volunteers ♂(Japanese)	Study EP06–108†: Double-blind Multiple dose (5 μg kg^{-1} × 2/day × 3 day) 34 healthy volunteers ♂(Japanese)
				Study EP06–110: Double-blind Multiple dose (5 μg kg^{-1} × 2/day × 3 day) 78 healthy volunteers ♂(Japanese)

All were randomized, two-period, crossover studies. *Stopped at stage 1 because of one severe anaphylactic reaction. †Out of the acceptance range of equivalency.

Table 5

Phase III studies of filgrastim BS submitted to the Japanese regulatory authorities (PMDA/MHLW)

	Filgrastim BS 'F' & 'Mochida'	Filgrastim BS 'NK' & 'Teva'	Filgrastim BS 'Sandoz'
Evaluation data	Study FSK0808P-02: ▪ single-arm, open-label ▪ primary endpoint: efficacy (DSN) ▪ 104 breast cancer patients receiving 5FU, EPI & CPA (Japanese)		
Reference data*		Study XM02–02-INT: ▪ randomized, single-blind ▪ primary endpoint: efficacy (DSN) ▪ 348 breast cancer patients receiving DTX/DXR (non-Japanese/BS:140, P:72, Neupogen:136)	Study EP06–301: ▪ single-arm, open-label ▪ primary endpoint: safety, tolerability & immunogenicity ▪ 170 breast cancer patients receiving DTX/DXR (non-Japanese)
		Study XM02–03-INT: ▪ randomized, single-blind ▪ primary endpoint: safety ▪ 237 lung cancer patients receiving platinum-based chemotherapy (non-Japanese/BS: 158, Neupogen: 79)	
		Study XM02–04-INT: ▪ randomized, single-blind ▪ primary endpoint: safety ▪ 92 non-Hodgkin lymphoma receiving CHOP (non-Japanese/BS: 63, Neupogen: 29)	

DSN, duration of severe neutropenia. *Safety only was evaluated.

Table 6

Phase III studies of filgrastim BS submitted to EMA

	Biograstim, Ratiograstim, Tevagrastim	Filgrastim Hexal, Zarzio	Nivestim	Accofil, Grastofil
Single-arm study		Study EP06–301: ▪ primary endpoint: safety, tolerability & immunogenicity ▪ 170 breast cancer patients receiving DTX & DXR		Study KWI-300-104: ▪ primary endpoint: safety ▪ 120 breast cancer patients receiving DTX, DXR & CPA
Comparative study	Study XM02–02-INT: ▪ randomized, single-blind ▪ primary endpoint: efficacy (DSN) ▪ 348 breast cancer patients receiving DTX & DXR (BS: 140, P: 72, Neupogen: 136)		Study GCF071: ▪ randomized, double-blind ▪ primary endpoint: efficacy (DSN) ▪ 279 breast cancer patients receiving DTX & DXR (BS: 184, Neupogen: 95)	
	Study XM02–03-INT: ▪ randomized, single-blind ▪ primary endpoint: safety ▪ 237 lung cancer patients receiving platinum-based chemotherapy (BS: 158, Neupogen: 79)			
	Study XM02–04-INT: ▪ randomized, single-blind ▪ primary endpoint: safety ▪ 92 non-Hodgkin lymphoma receiving CHOP (BS: 63, Neupogen: 29)			

DSN, duration of severe neutropenia.

Table 7

Clinical data package of infliximab BS approved

	Design	Primary endpoint	Study population	Number of patients randomized	Dosage	Japan	EU	Canada
Study B1P13101	Randomized double-blind, parallel-group, comparative	AUC Cmax	Rheumatoid arthritis (Japanese)	BS + MTX: 39 EU Remicade + MTX: 39	Multiple IV (3 mg kg^{-1})	○		
Ph I (pilot), Study CT-P13 1.2	Randomized double-blind, parallel-group, comparative	Cmax	Rheumatoid arthritis (non-Japanese)	BS + MTX: 9 Remicade + MTX: 10	Multiple IV (3 mg kg^{-1})	△*	○	○*
Ph I, Study CT-P13 1.1 (PLANET AS)	Randomized double-blind, parallel-group, comparative	AUC Cmax	Ankylosing spondylitis (non-Japanese)	BS: 125 Remicade: 125	Multiple IV (5 mg kg^{-1})	△*	○	○
Ph III, Study CT-P13 3.1 (PLANET RA)	Randomized double-blind, parallel-group, comparative	ACR20 (Week 30)	Rheumatoid arthritis (non-Japanese)	BS + MTX: 302 Remicade + MTX: 304	Multiple IV (3 mg kg^{-1})	○	○	○

○, Evaluation data. △, reference data. *Safety only was evaluated.

Insulin glargine BS

The clinical similarity of insulin glargine BS to the reference product Lantus was demonstrated by comparative PK/PD studies using the euglycemic clamp method (Table 8) [9, 25]. Japanese patients were not included in any of the comparative PK/PD studies. Study ABEA, which was conducted to demonstrate the PK equivalence between insulin glargine BS and the EU-approved Lantus, was provided as the evaluation data for the Japanese MAA. In addition to PK/PD studies, two Phase III studies (non-inferiority studies) were conducted and the ABEN study, a global clinical trial including Japanese Type 1 diabetes mellitus patients, was provided as the evaluation data for the Japanese MAA (Table 9).

Table 8

Comparative PK/PD studies of insulin glargine BS

	Design	Primary endpoint	Products administered	Dosage	Study population	No. of randomized subjects	Japan	EU
Study ABEA	Randomized, double-blind, 4-period, crossover, glucose clamp study	AUC, C_{max} GIR_{AUC}, GIR_{max}	BS⇔EU Lantus (0.5 U kg^{-1})	Single SC	Healthy subject (non-Japanese)	80	○	○
Study ABEO	Randomized, double-blind, 4-period, crossover, glucose clamp study	(AUC, C_{max} GIR_{AUC}, GIR_{max})	BS⇔US Lantus (0.5 U kg^{-1})	Single SC	Healthy subject (non-Japanese)	91	△	○
Study ABEN	Randomized, double-blind, 4-period, crossover, glucose clamp study	AUC, C_{max} GIR_{AUC}, GIR_{max}	EU Lantus⇔ US Lantus (0.5 U kg^{-1})	Single SC	Healthy subject (non-Japanese)	40	△	○
Study ABEI	Randomized, open-label, 2-period, crossover, glucose clamp study	AUC, C_{max} GIR_{AUC}, GIR_{max}	BS⇔EU Lantus (0.5 U kg^{-1})	Single SC	Healthy subject (non-Japanese)	16	△	△
Study ABEM	Randomized, double-blind, 4-period, crossover, glucose clamp study	AUC, C_{max} GIR_{AUC}, GIR_{max}	BS⇔EU Lantus (0.3 U kg^{-1}, 0.6 U kg^{-1})	Single SC	Healthy subject (non-Japanese)	24	△	△
Study ABEE	Randomized, double-blind, 2-period, crossover, glucose clamp study	AUC, C_{max} GIR_{AUC}, GIR_{max}	BS⇔EU Lantus (0.3 U kg^{-1})	single SC	Patients with T1DM (non-Japanese)	20	△	△

○, Evaluation data. △, reference/supportive data.

Table 9

Phase III studies of insulin glargine BS

	Design	Primary endpoint	Study population	Number of patients randomized	Dosage	Treatment duration	Japan	EU
Study ABEB	Randomized, active -control, open-label, parallel	Change in HbA1c from baseline (non-inferior)	Patients with T1DM (including Japanese)	BS:268 Lantus:267	SC Once daily (with insulin lispro)	24 week+ 28 week (extension)	○	○
Study ABEC	Randomized, active -control, double-blind, parallel	Change in HbA1c from baseline (non-inferior)	Patients with T2DM (non-Japanese)	BS:376 Lantus:380	SC Once daily	24 week	△	○

○, Evaluation data. △, reference/supportive data.

Extrapolation of indications

Reference products may have more than one indication. The Japanese guideline states that when biosimilar comparability has been demonstrated for one indication, it may be possible to extrapolate from clinical data to other indications of the reference products if the equivalent effects can be expected pharmacologically [2], as is the case in other regions/countries.

Somatropin BS

In Japan, somatropin BS has been approved for three indications: GHD in paediatric patients, Terner Syndrome and chronic renal insufficiency, although the subjects for the Phase III studies were only a GHD paediatric group [3, 16]. The re-examination/exclusive periods of these indications of the reference product Genotropin had expired, and it was decided that it was possible to extrapolate the clinical data to other indications where the equivalent effects can be expected based on the pharmacological actions, as described [3, 16]. When the re-examination/exclusive period of 'GHD in adults' of the reference products expired in 2011 and those of 'Prader-Willi Syndrome' and 'Small for gestational age' expired in 2013, these indications were approved after the review of the possibility of extrapolation.

Epoetin alfa BS

Epoetin alfa BS 'JCR' has been approved for two indications: renal anaemia in dialysis and anaemia of prematurity, although the subjects for the Phase III studies were only renal anaemia patients on haemodialysis, as the extrapolation of clinical data to other indications based on the pharmacological actions was

considered acceptable (Table 10) [4]. Epoetin alfa BS and epoetin zeta have also been approved in the EU for not only renal anaemia in dialysis and anaemia caused by cancer chemotherapy, for which clinical trials were conducted, but also other indications, which the reference products Eprex/Erypo have [17, 18].

Filgrastim BS

All filgrastim BS products in Japan have been approved with all of the indications for Gran, as the clinical similarity of filgrastim BS was demonstrated by comparative PK/PD studies and the re-examination/exclusive periods of all indications for Gran have expired (Table 11) [5–7].

Infliximab BS

In Japan, although the subjects in a PK study in Japan and a Phase III study were only RA patients, the indications of Crohn's disease (CD) and ulcerative colitis (UC), the re-examination/exclusive periods of which had expired for the reference product Remicade, were also approved in addition to RA [8]. In the review report from Japan, it was decided that the extrapolation of the data was acceptable (Table 12), for the following reasons:

1. High similarity between infliximab BS and Remicade was identified in the quality tests and non-clinical studies.
2. The membrane-bound tumour necrosis factor-alpha (TNFα)-mediated biological activities (i.e., antibody-dependent cell-mediated cytotoxicity [ADCC], complement-dependent cytotoxicity [CDC] and apoptosis) that are considered important in granulomatous diseases such as CD were similar, in addition to neutralizing activity against TNFα.

The indications of 'psoriasis' and 'psoriatic arthritis' were approved when their re-examination/exclusive period of the reference products had expired in 2015.

In the EU, infliximab BS was also approved for all of the indications that the reference product has even though only studies of RA patients and AS patients are included in the clinical data package [23].

In Canada, extrapolation from RA and ankylosing spondylitis to inflammatory bowel diseases (IBD) was not recommended as differences in the ADCC have been observed between the two products and because ADCC may be an active mechanism of action for infliximab in IBD, but not in rheumatic disease [24, 26]. However, in the review report from Japan, the ADCC activities of infliximab BS and Remicade were 105% and 110%, respectively, and the Japanese regulatory authority concluded that differences in ADCC have not been observed [7].

Issues regarding the development of biosimilar products in Japan

Reference products

The Japanese guideline states that for the development of a biosimilar product, a reference product must be approved in Japan and a single reference product should be used during the development of the biosimilar product [2]. However, the reference product used in the Phase I study of infliximab BS conducted in Japan is Remicade from the EU market [8], as it may be difficult to obtain a reference product from the Japanese market. The reference product used in the clinical studies of insulin glargine BS is not Lantus from the Japanese market [9]. Basically, it is not disclosed whether the manufacturing sites, manufacturing process and specification of reference products approved in Japan and another country are the same. Therefore, the data from analytical studies that compare a biosimilar, a Japan-authorized reference product and a non-Japan-authorized reference product are included, but clinical bridging data are not included for infliximab BS [8] or insulin glargine BS [9]. In the review report of both products from Japan, it is noted that the reference products from overseas markets are similar to those from the Japanese market as shown by an analytical

Table 10

Indication for epoetin alfa BS approved

		Epoetin Alfa BS 'JCR'			Abseamed, Binocrit, Epoetin alfa Hexal			Retacrit, Silapo		
		Ref.	Ph III	Approved	Ref.	Ph III	Approved	Ref.	Ph III	Approved
Renal anemia on dialysis	Haemodialysis		○			○			○	
	Peritoneal dialysis	○		○	○		○	○		○
	Maintenance phase		○			○			○	
	Correction phase					○				
Renal anemia not yet undergoing dialysis					○		○	○		○
Anemia of prematurity		○		○						
Autologous blood predonation					○		○*	○		○
Cancer chemotherapy-induced anemia					○	○	○	○	○	○
Orthopedic surgery					○		○	○		○*

Ref., Indication of reference product. *Added since initial authorization.

Table 11

Indication for filgrastim BS approved in Japan

Product / Indication		Ref.	Filgrastim BS 'F' and Mochida PD marker	Ph III	Approved	Filgrastim BS 'NK' and Teva PD marker	Ph III	Approved	Filgrastim BS 'Sandoz' PD marker	Ph III	Approved
Mobilization of PBPC		○	CD34 C_{max} CD34 t_{max}		○	CD34 AUEC CD34 C_{max}		○	CD34 AUEC CD34 E_{max}		○
Increase in neutrophils in haematopoietic stem cell transplant		○			○			○			○
Neutropenia with cancer chemotherapy	**Acute leukemia**	○			○			○			○
	Malignant lymphoma	○			○		R	○			○
	Others	○	ANC C_{max}	E	○	ANC AUEC	R	○	ANC AUEC	R	○
Neutropenia to impair treatment of HIV infection		○	ANC t_{max}		○	ANC C_{max}		○	ANC E_{max}		○
Neutropenia with the marrow dysplasia syndrome		○			○			○			○
Neutropenia with aplastic anemia		○			○			○			○
Congenital/idiopathic neutropenia		○			○			○			○

Ref., Indication of reference product. E, Evaluation data. R, reference/supportive data.

Table 12

Indications approved for infliximab BS

	Clinical study conducted	Remicade (Japan)	BS (Japan)	Remicade (EU)	BS (EU)	Remicade (Canada)	BS (Canada)
Rheumatoid arthritis	PK (Japan) PK (Pilot study) Ph III	○	○	○	○	○	○
Crohn's disease		○	○	○	○	○	×
Ulcerative colitis		○	○	○	○	○	×
Ankylosing spondylitis	PK study	○*	-	○	○	○	○
Psoriatic arthritis		○*	○†	○	○	○	○
Psoriasis		○*	○†	○	○	○	○
Behcet's disease-induced uveoretinitis		○*	-	-	-	-	-

*Re-examination/exclusive period had not expired at the initial authorization of infliximab BS. †Added when the re-examination/exclusive period of 'psoriasis' of the reference products expired

study. The necessity of clinical bridging data is not mentioned. According to the new Japanese Q&A, the use of reference products approved in foreign countries is acceptable if reference products approved in Japan and overseas can be demonstrated to be the same by mainly analytical study data.

In the EU, the bridging data including analytical studies that compare a biosimilar product, a European Economic Area (EEA)-authorized reference product and a non-EEA-authorized reference product are required in cases in which non-EEA-authorized reference products are used in clinical trials [27]. In addition, PK/PD bridging data may be required. This is described as well in the FDA's Q&A on biosimilars [28]. For example, clinical bridging data that compare a biosimilar, Lantus from the EU market and Lantus from the US market are included in the data package for the EU's MAA [25]. The data package of filgrastim BS in the US includes PK/PD studies using the US-licensed Neupogen in addition to the EU-approved Neupogen as a comparator, and a comparative Phase III study between the biosimilar and the US-licensed

Neupogen [12]. The extent of the requirement for bridging data between non-authorized reference products and authorized reference products seems to differ among regulatory agencies.

Necessity of Japanese data

Another challenge in the development of biosimilars in Japan concerns the necessity of Japanese data. In somatropin BS [3] and infliximab BS [8], comparative PK studies in Japanese patients were conducted in addition to the clinical data package for the MAA in other countries. The new Q&A states that either a comparative PK study or a Phase III study should include a Japanese population. The focus of such a biosimilarity exercise is to demonstrate similar efficacy and safety compared with reference products, and ethnic differences have already been demonstrated in some reference products; therefore, it is questionable whether the Japanese data are scientifically necessary.

For insulin glargine BS, biosimilarity was evaluated in not only the entire population but also the Japanese subpopulation of a global Phase III study [9]. When global clinical trials are conducted for biosimilar development, it is more important to equally allocate patients to two arms based on the factors affecting the evaluation (e.g., a Japanese population if there is an ethnic difference) which were identified in the development of the reference product, rather than ensuring the number of Japanese cases.

Different indications and dosages of reference products

The Japanese guideline [2] and the new Q&A [10] require that the clinical studies for a biosimilar product are conducted for the same indications and using the same dosages of the reference product. When the indications and dosages of the reference product differ between Japan and other countries, it is difficult for Japan to participate in global clinical studies and additional Japanese data are required. Since the focus of clinical studies for biosimilar development is to demonstrate similarity in adequate populations, it may be possible in theory for Japanese patients to participate in global clinical trials carried out using indications or dosages not approved in Japan if doing so would not create safety concerns.

PK study

Comparative PK studies by all routes of administrations used in the reference product are required in the Japanese guideline [2] and the EU annex guideline for granulocyte-colony stimulating factor (G-CSF) [29]. Comparative PK studies of all of the filgrastim BS products were conducted using both IV and SC administration in Japan [5–7] and the EU [19–22]. However, the revised EU guideline for non-clinical and clinical issues [30] and the new Japanese Q&A [10] state that if the reference product can be administered by both IV and SC routes, the evaluation of SC administration will usually be sufficient as it covers both absorption and elimination. The US guidance states that comparative PK studies should use a route of administration that is adequately sensitive [13]; thus, all PK/PD studies of Zarxio for the US's MAA were conducted by only SC administration [12]. These revisions in the EU and Japan would lead to the efficient development of biosimilar products.

Non-inferiority study design

In general, an equivalence design should be used in comparative clinical studies for biosimilar development. The non-inferiority study design is not mentioned in the Japanese guidelines [2] or the new Q&A [10], whereas in the revised EU guideline [30] and the US guidance [13], it is stated that a non-inferiority trial alone may be accepted in some cases. Comparative Phase III studies of insulin glargine BS had a non-inferiority study design but clinical comparability was demonstrated by comparative PK/PD studies [9]. Therefore, none of the biosimilar products for which the pivotal studies are not equivalence design have been approved. It is a future challenge to determine which cases would be acceptable for non-inferiority studies.

Sensitive clinical model

It has been pointed out in the EU guidelines [30], the US guidance [13] and the new Japanese Q&A [10] that a study's population should be sensitive for detecting potential differences between the biosimilar and the reference product. A monoclonal antibody-specific guideline from the EMA states that a single-dose study in healthy volunteers is recommended for comparative PK studies as healthy volunteers are likely to show less variability in PK as target-mediated clearance [31]. However, comparative PK studies of infliximab BS have been conducted in patients in Japan [8] and other countries [23, 24]. With respect to immunogenicity, it is noted in the review report of epoetin alfa BS that an extrapolation of immunogenicity data from IV to SC use or from immunocompromised (oncology) to immunocompetent (chronic kidney disease [CDK]) patients was not possible as the risk of anti-epoetin antibody-induced pure red cell aplasia (PRCA) is highest with SC use in CKD patients [17]. Therefore, the EMA concluded that the risk–benefit ratio of epoetin alfa BS for SC use in CKD patients was unfavourable due to the lack of adequate immunogenicity data in CKD patients (SC). On the other hand, no immunogenicity data of repeated SC use is included in the data package in Japan but it was decided that the extrapolation of the data of CKD patients (IV) to patients with anaemia in prematurity (SC) was acceptable [4]. Thus, each regulatory agency's requirements of clinical study data in a sensitive population may differ.

Conclusion

This article has focused on the clinical data packages of biosimilar products and the issues of biosimilar development in Japan, including the reference products, the necessity of Japanese data, the acceptability of the non-inferiority study design and sensitive clinical models. No major difference in the concepts used by the regulatory authorities for the clinical data of biosimilar products was revealed except that the Japanese regulatory authority, PMDA, requires data from Japanese subjects. In addition, the extent of the requirement for clinical data in a sensitive clinical model and for bridging

data between non-authorized reference products and authorized reference products seems to differ among regulatory agencies. The acceptability of non-inferiority studies is not clear in Japan. The new Japanese Q&A is helpful for understanding the concepts regarding these points but several challenges remain. It is necessary to explain the detailed approval requirements for the development of biosimilars so that many types of biosimilar products can become available for patients.

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